Armed Forces College of Medicine

AFCM

Sphingolipidoses 2

Dr. Naglaa Fathy, MD

INTENDED LEARNING OBJECTIVES (ILOs)

- **By the end of this lecture, You will be able to:**

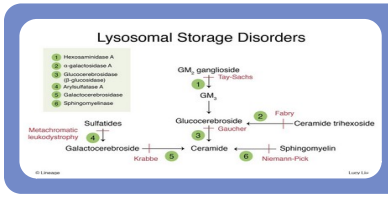
1. **Correlate enzyme deficiency to different types of sphingolipidoses**
2. **Outline the strategy of diagnosis and treatment of sphingolipidoses**

Contents:

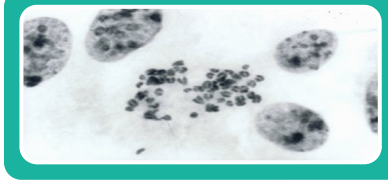
GM2 Catabolism & Tay- Sachs disease

Glucocerebroside catabolism & Gaucher's disease

Sphingomyelin Catabolism & Niemann-Pick disease

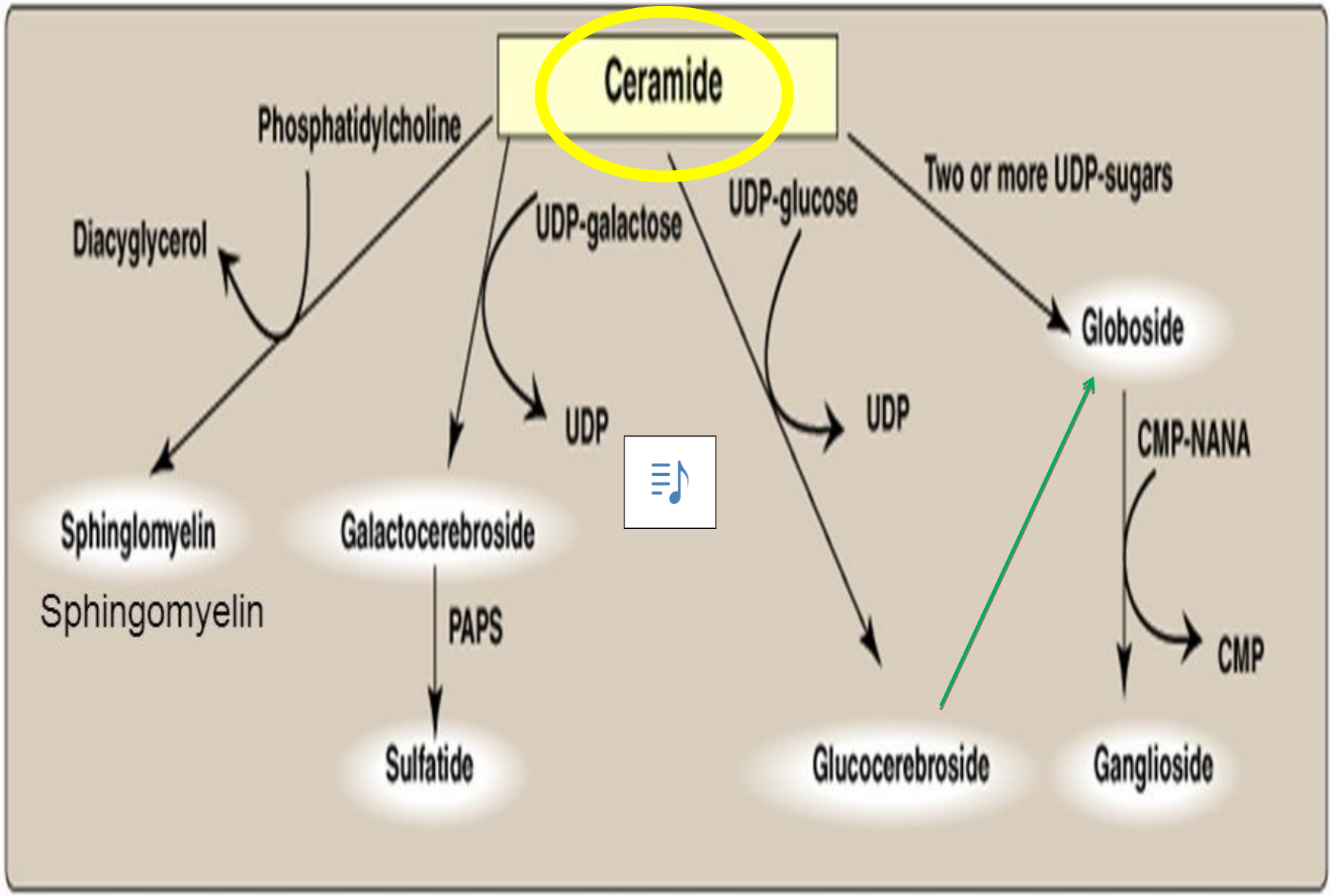


Other Lipid Storage Diseases



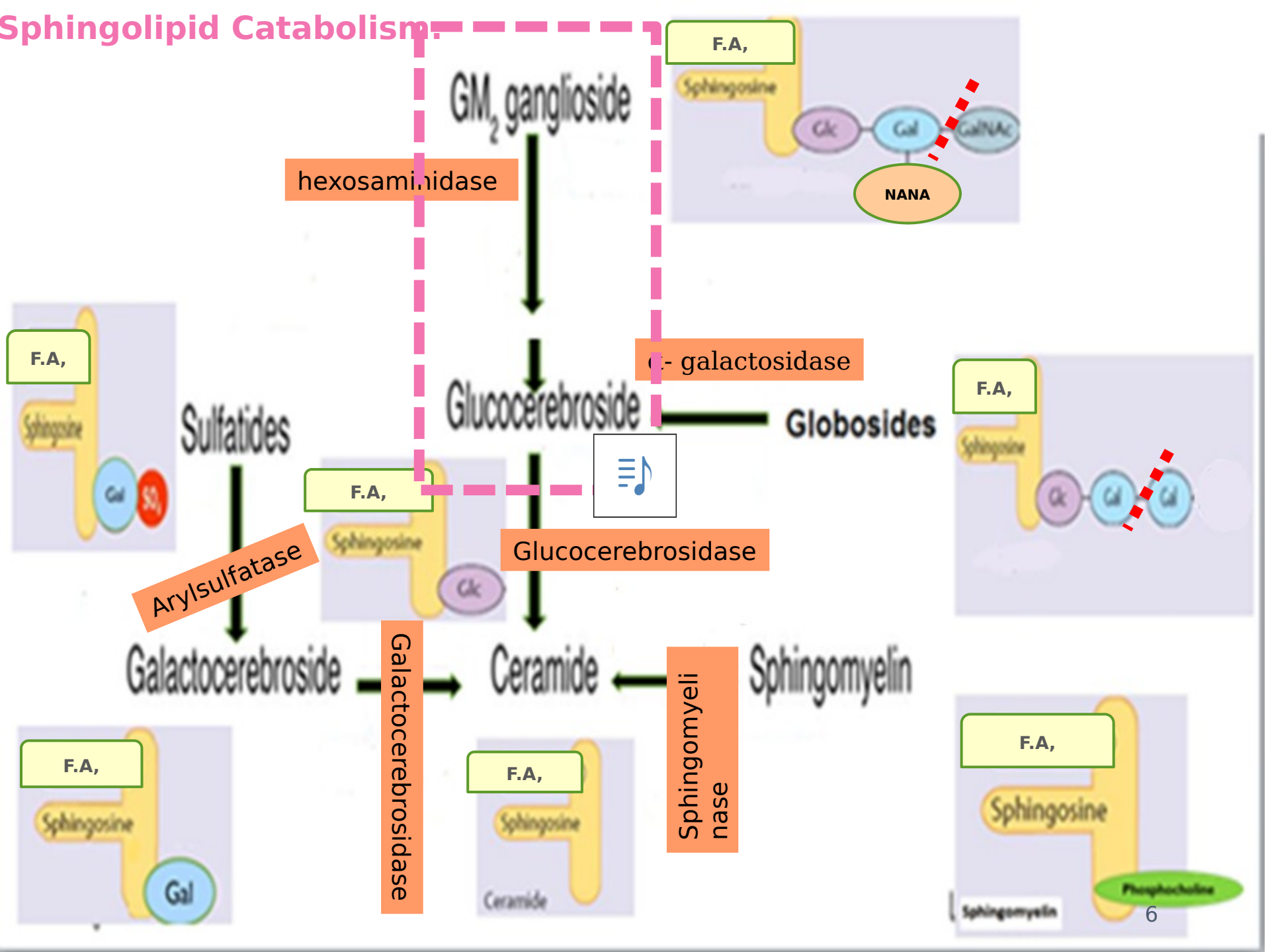
Diagnosis of Sphingolipidoses

Treatment of Sphingolipidoses

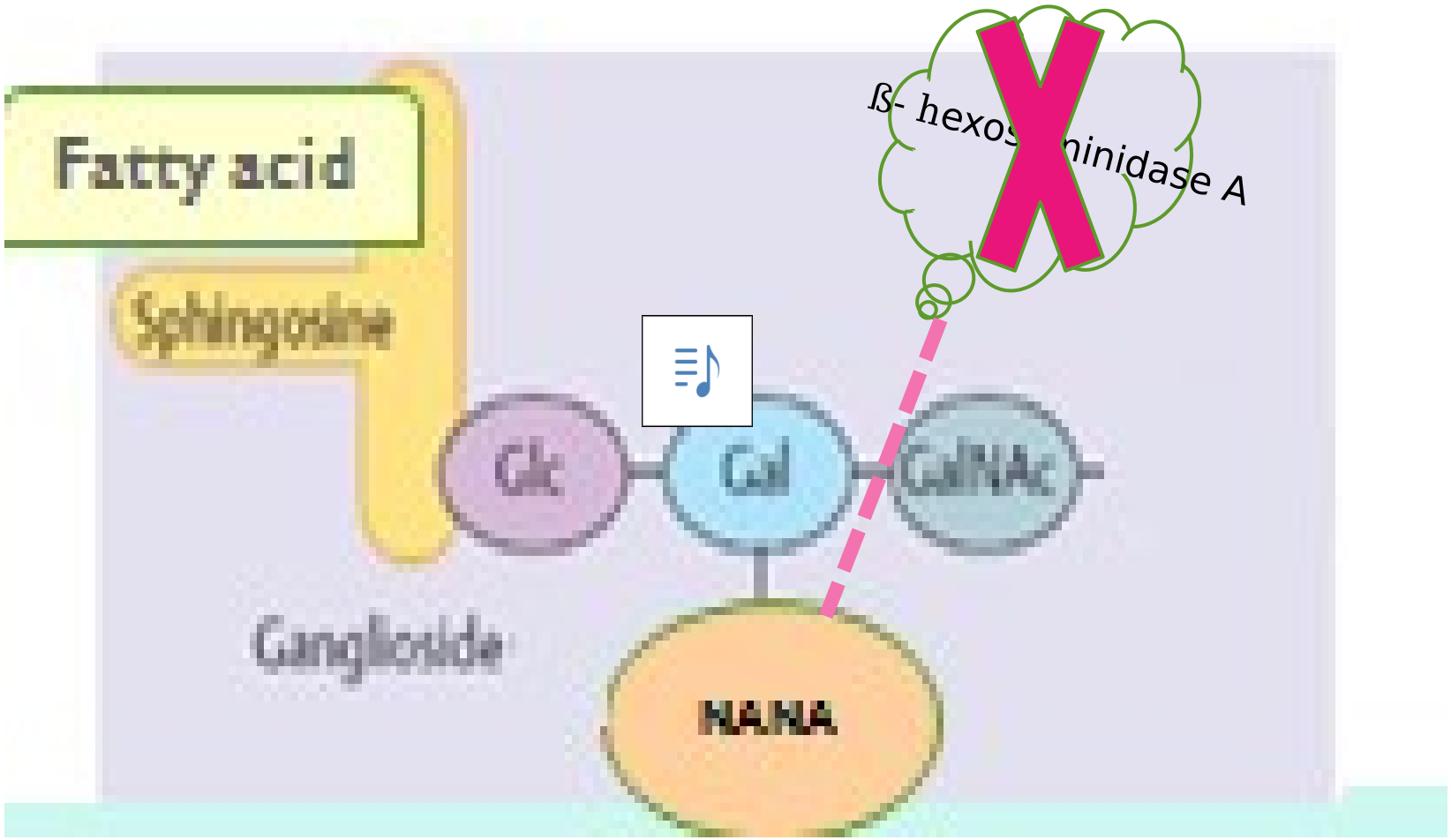


Lippincott's Illustrated Reviews: Biochemistry, Sixth Edition (2014) P. 214 (Edited with the green arrow)

Sphingolipid Catabolism:



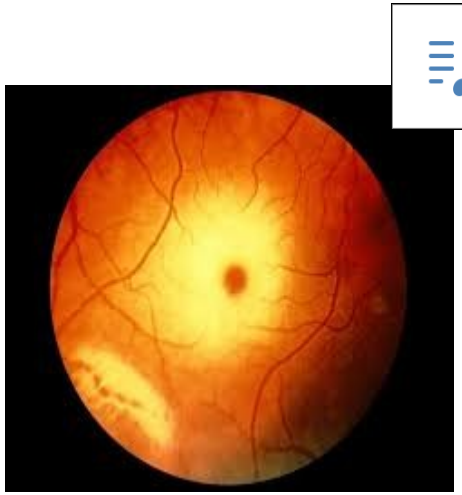
GM_2 Catabolism & Tay- Sachs disease:



Tay- Sachs disease:

- **Defective lysosomal Enzyme: ? ? ? ? ? ? ?**
- **Accumulated substrate: ? ? ? ? ?**
- **Manifestations: ? ? ? ? ? ? ?**

https://www.dailylocal.com/news/national/irish-ancestry-focus-of-tay-sachs-families/article_e01ba0d2-3f50-5a60-a699-bbe5a3e63ba6.html



https://edu.glogster.com/glog/tay-sachs-worst-disease-ever/1nk3813lu9d

https://www.tes.com/lessons/CF4C8RaH1kB8ng/group-13-625-624-tay-sachs-disease

https://en.wikipedia.org/wiki/Tay%E2%80%93Sachs_disease

Tay- Sachs disease:

- **Defective lysosomal Enzyme:** Hexosaminidase A

- **Accumulated substrate:** Ganglioside GM2

- **Manifestations:**

Rapidly progressing Mental retardation & Blindness

Cherry-red macula

Muscular weakness & Seizures

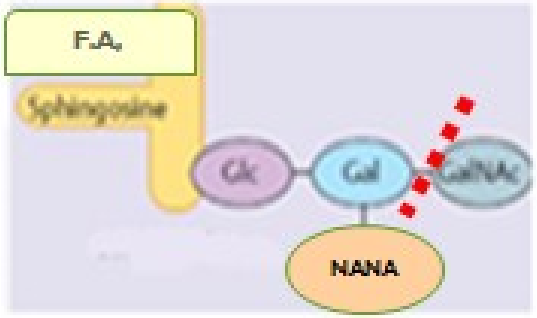
Early mortality

MCQ

A 9-month-old infant presented with spastic movements and doesn't respond well to visual stimuli. Ophthalmologic examination revealed cherry-red spots at the macula. **A defect in which of the following was most likely present in this infant?**

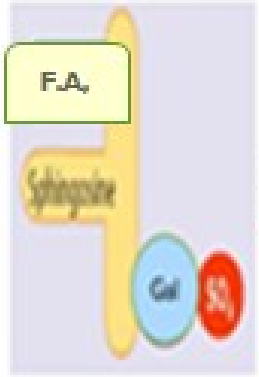
A. Degradation of glycogen
B. Degradation of ganglioside GM2
C. Degradation of glucocerebrosides
D. Degradation of sphingomyelin
E. Synthesis of gangliosides

Sphingolipid Catabolism:



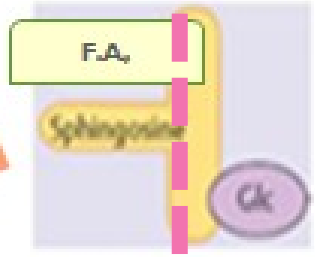
GM_2 ganglioside

hexosaminidase



Sulfatides

Arylsulfatase



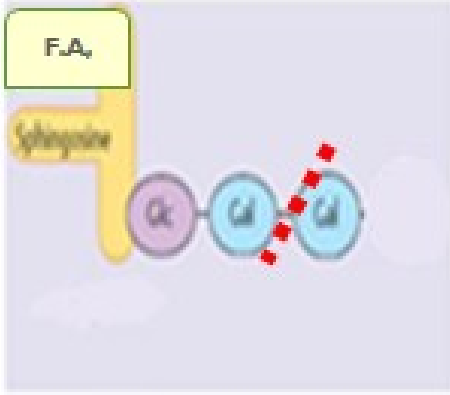
Galactocerebroside

Galactocerebrosidase

Glucocerebroside

α- galactosidase

Globosides

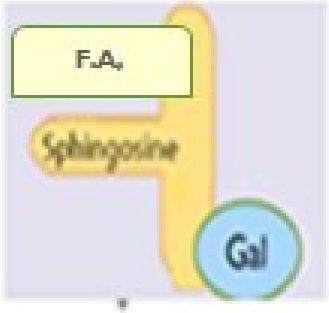


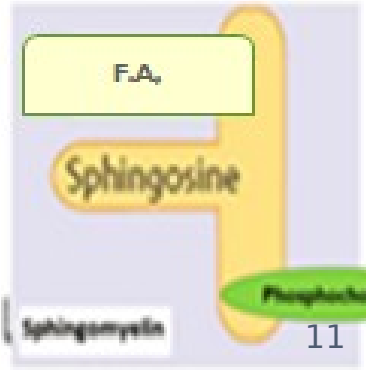
Glucocerebrosidase

Ceramide

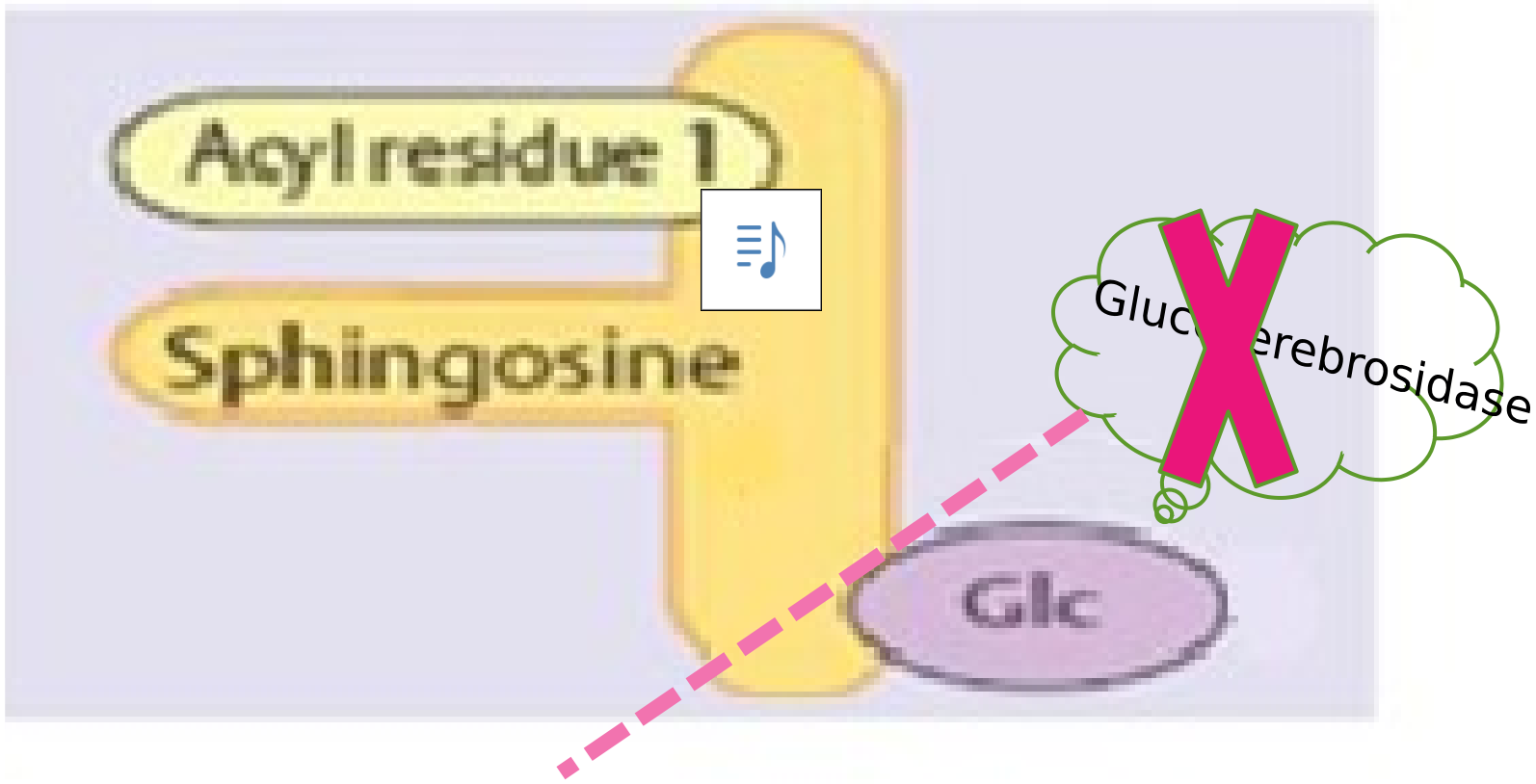
Sphingomyelinase

Sphingomyelin



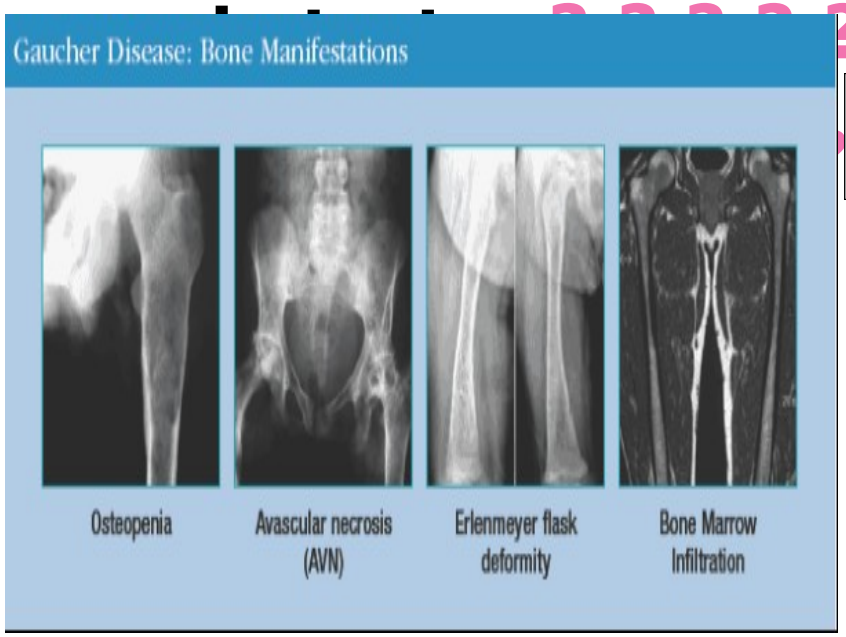


Glucocerebroside catabolism & Gaucher's disease:

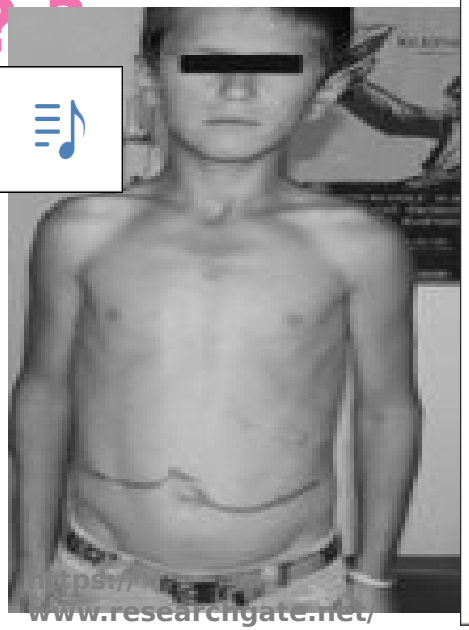


Gaucher's disease:

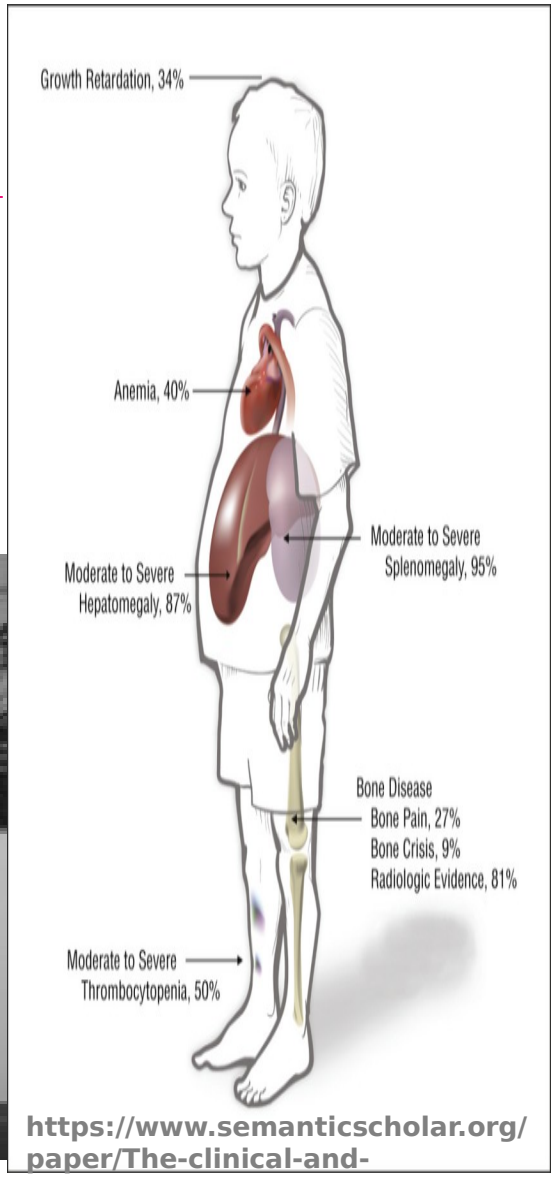
- **Defective lysosomal Enzyme:** ? ? ? ? ?
- **Accumulated**



https://nursinganswers.net/essays/gauchers-disease-types-symptoms-9417.php



https://www.researchgate.net/publication/26795434_Type_I_Gaucher_disease_GDI_in_three_siblings_enzyme_replacement_treatment_ERT_required

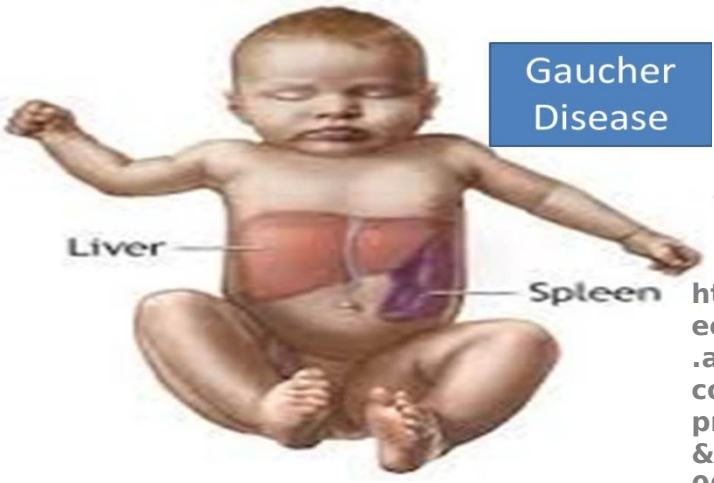


https://www.semanticscholar.org/paper/The-clinical-and-demographic-characteristics-of-in-Kaplan-Andersson/28f6bcbd925328c4eb7baab945c58c11e56b8196/figure/3

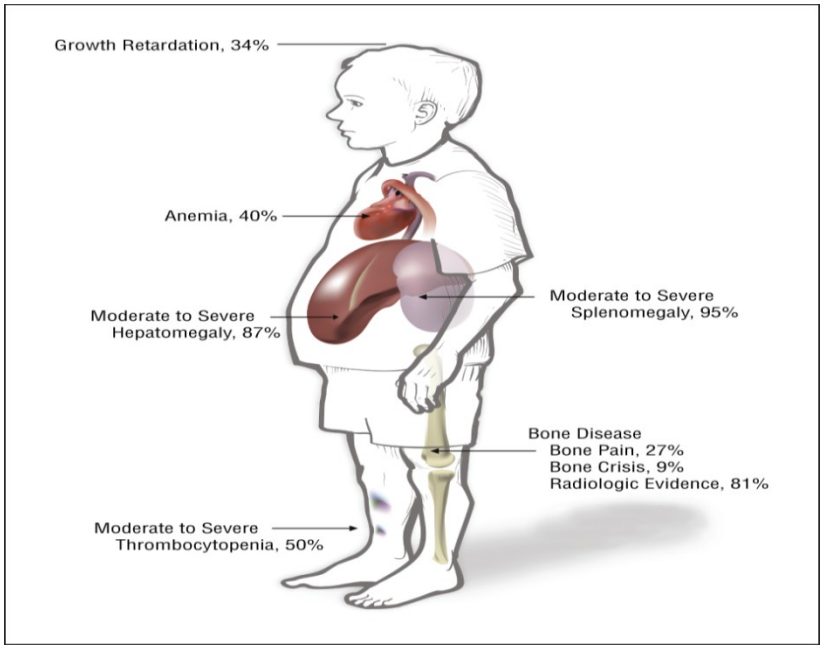
Gaucher's disease

- **Defective lysosomal Enzyme:**
  β –Glucocerebrosidase

- **Accumulated Substrate:** Glucocerebrosides
  - **Manifestations:**
    Hepatosplenomegaly
    Pancytopenia or Thrombocytopenia
    Long bone degeneration
    mental retardation in infantile form only



http://eclinicalworks.adam.com/content.aspx?productId=39&pid=1&gid=000564&print=1



https://www.semanticscholar.org/paper/The-clinical-and-demographic-characteristics-of-in-Kaplan-Andersson/28f6bcbd925328c4eb7baab945c58c11e56b8196/figure/3

MCQ

The defective enzyme in Gaucher's disease results in defective:

A. Degradation of glycogen

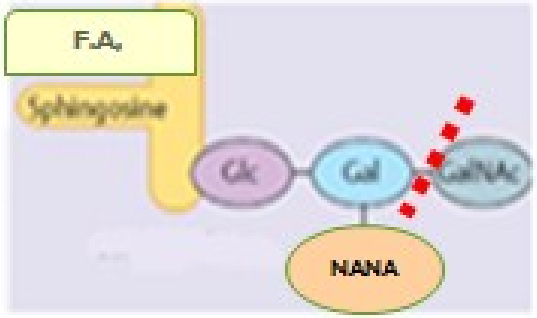
B. Degradation of ganglioside GM2

C. Degradation of glucocerebrosides

D. Degradation of sphingomyelin

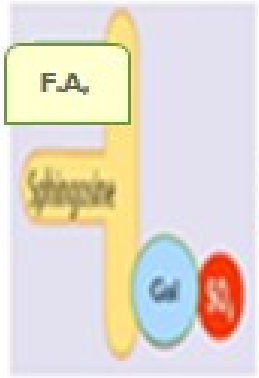
E. Synthesis of gangliosides

Sphingolipid Catabolism:

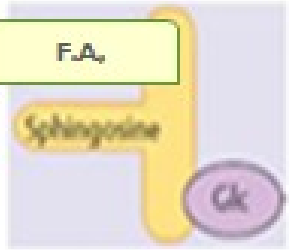


GM_2 ganglioside

hexosaminidase



Sulfatides

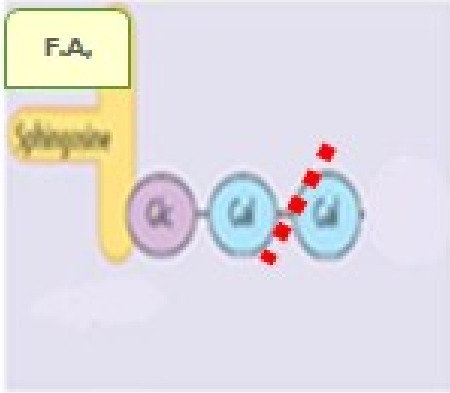


Arylsulfatase

Glucocerebroside

α- galactosidase

Globosides



Glucocerebrosidase

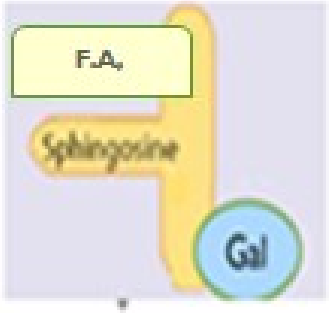
Galactocerebroside

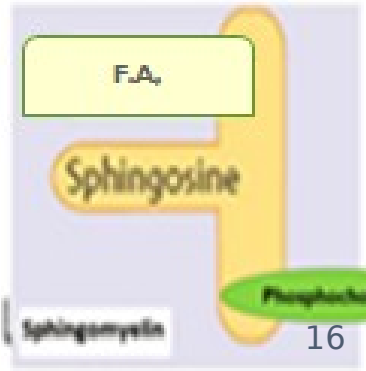
Galactocerebrosidase

Ceramide

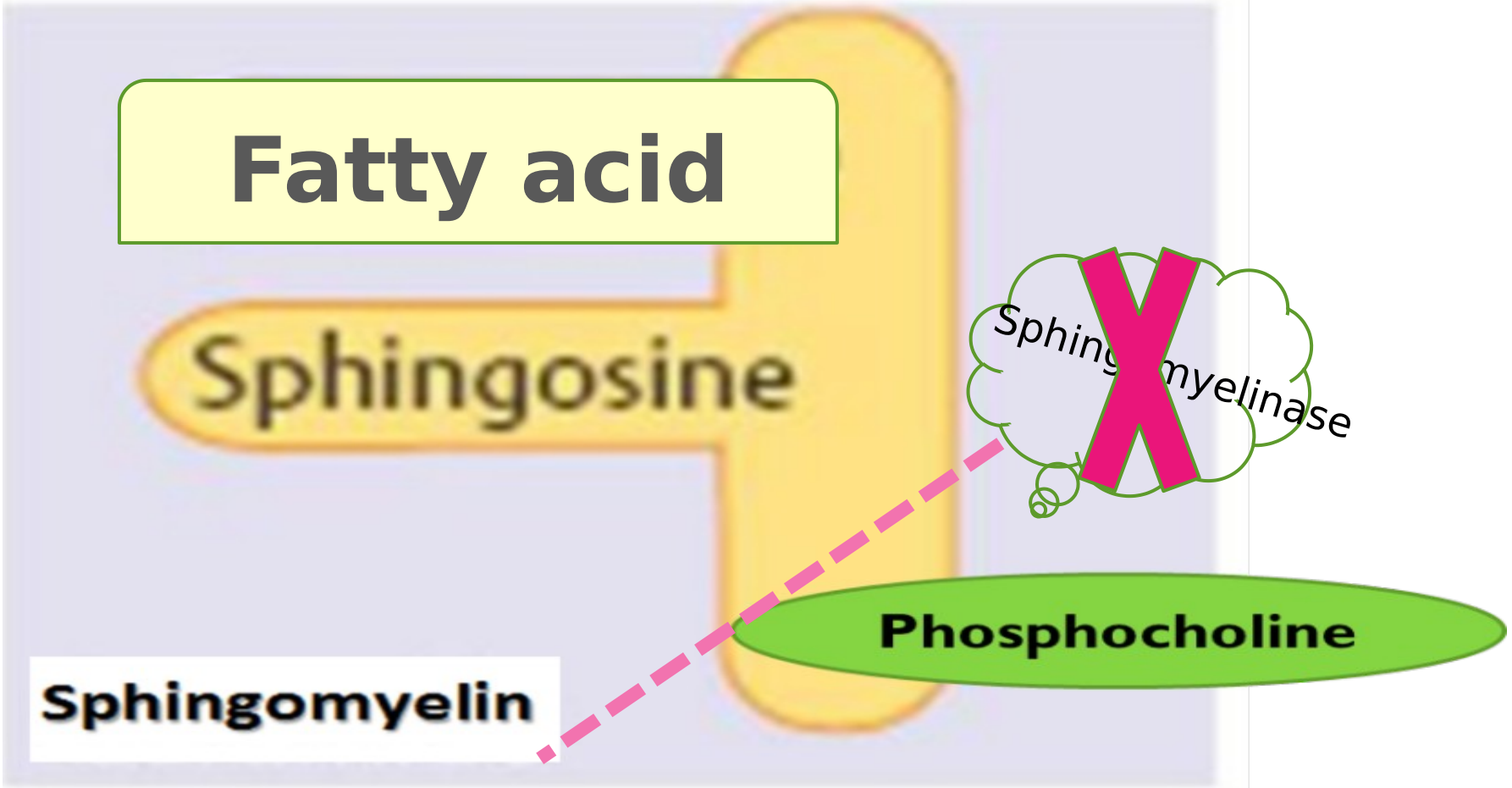
Sphingomyelinase

Sphingomyelin





Sphingomyelin Catabolism & Niemann-Pick disease:



Niemann-Pick disease:

- **Defective lysosomal Enzyme: ? ? ? ? ? ? ?**
- **Accumulated substrate: ? ? ?**
- **Manifestations: ? ? ? ? ? ? ?**

https://edition.cnn.com/2014/11/21/health/hempels-genetic-disorder-niemann-pick/index.html

https://nnpdf.org/day-6-october-2015-global-niemann-pick-disease-awareness-month/

https://www.semanticscholar.org/paper/Spectrum-of-SMPD1-mutations-in-Asian-Indian-with-Ranganath-Matta/7837207b13a2f1301769987bd5c6bb7fb8d9d16f

Niemann-Pick disease:

- **Defective lysosomal Enzyme:**
  Sphingomyelinase

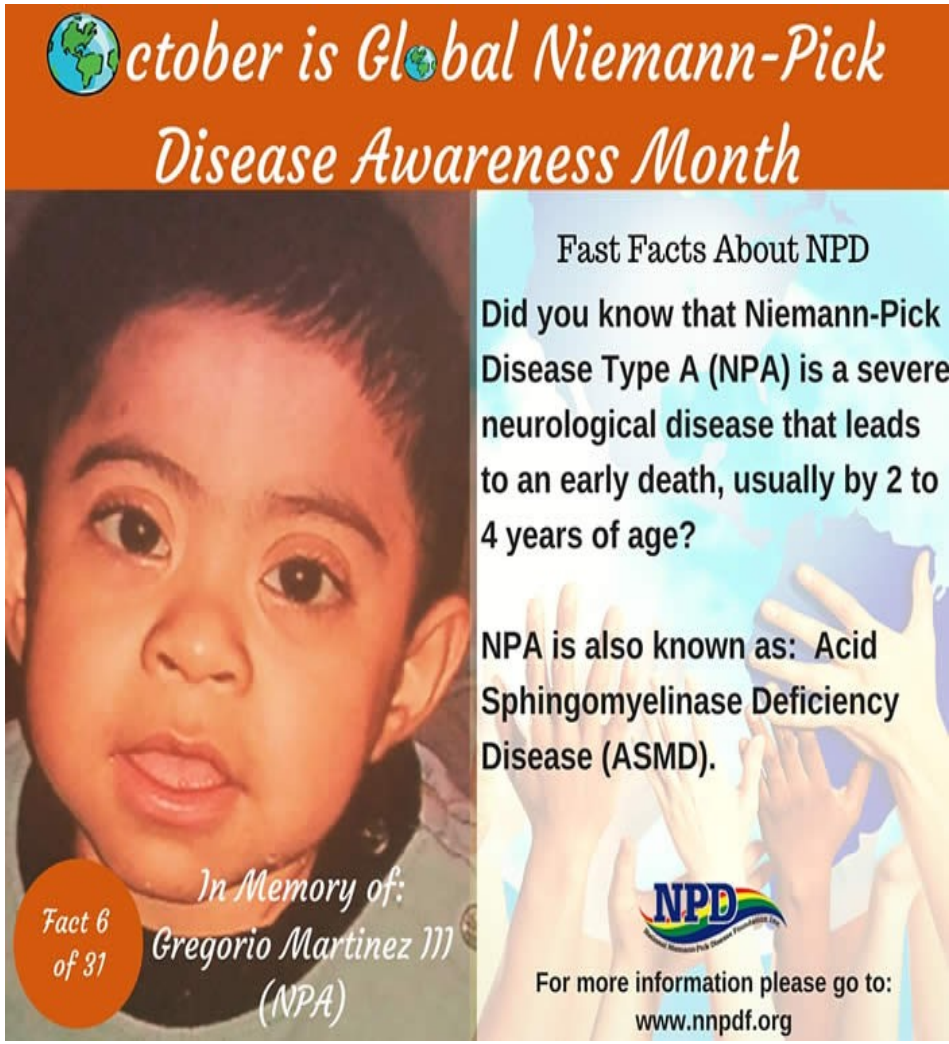
- **Accumulated substrate:**
  Sphingomyelin.

- **Manifestations:**

  Mental retardation

  Hepatosplenomegaly

  Early death (A- type)


ctober is Global Niemann-Pick Disease Awareness Month
Fact 6 of 31
In Memory of:
Gregorio Martinez III
(NPA)
Fast Facts About NPD
Did you know that Niemann-Pick Disease Type A (NPA) is a severe neurological disease that leads to an early death, usually by 2 to 4 years of age?
NPA is also known as: Acid Sphingomyelinase Deficiency Disease (ASMD).
NPD
For more information please go to:
www.nnpdf.org

https://nnpdf.org/day-6-october-2015-global-niemann-pick-disease-awareness-month/

MCQ

Mental retardation accompanying Niemenn- Pick disease is due to accumulated which of the following in the CNS?

A. Degradation of glycogen

B. Degradation of ganglioside GM2

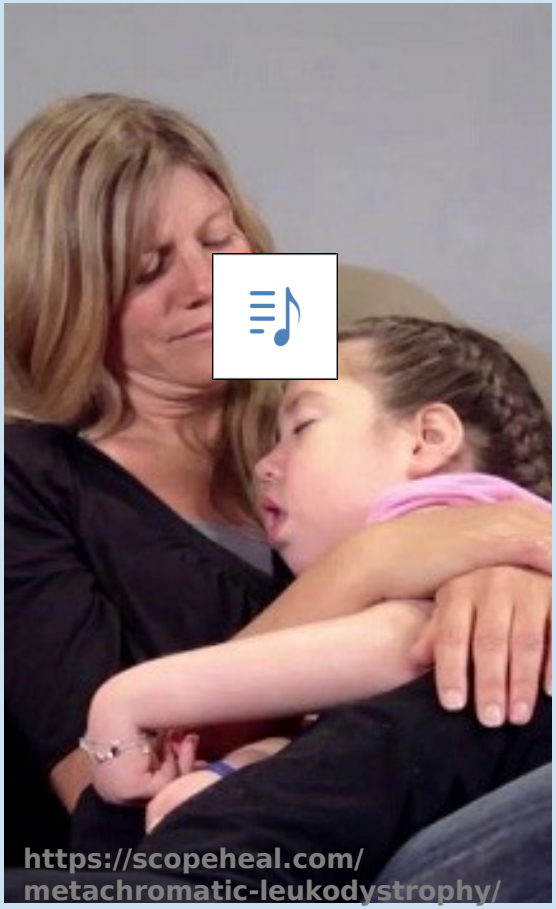
C. Degradation of glucocerebrosides

D. Degradation of sphingomyelin

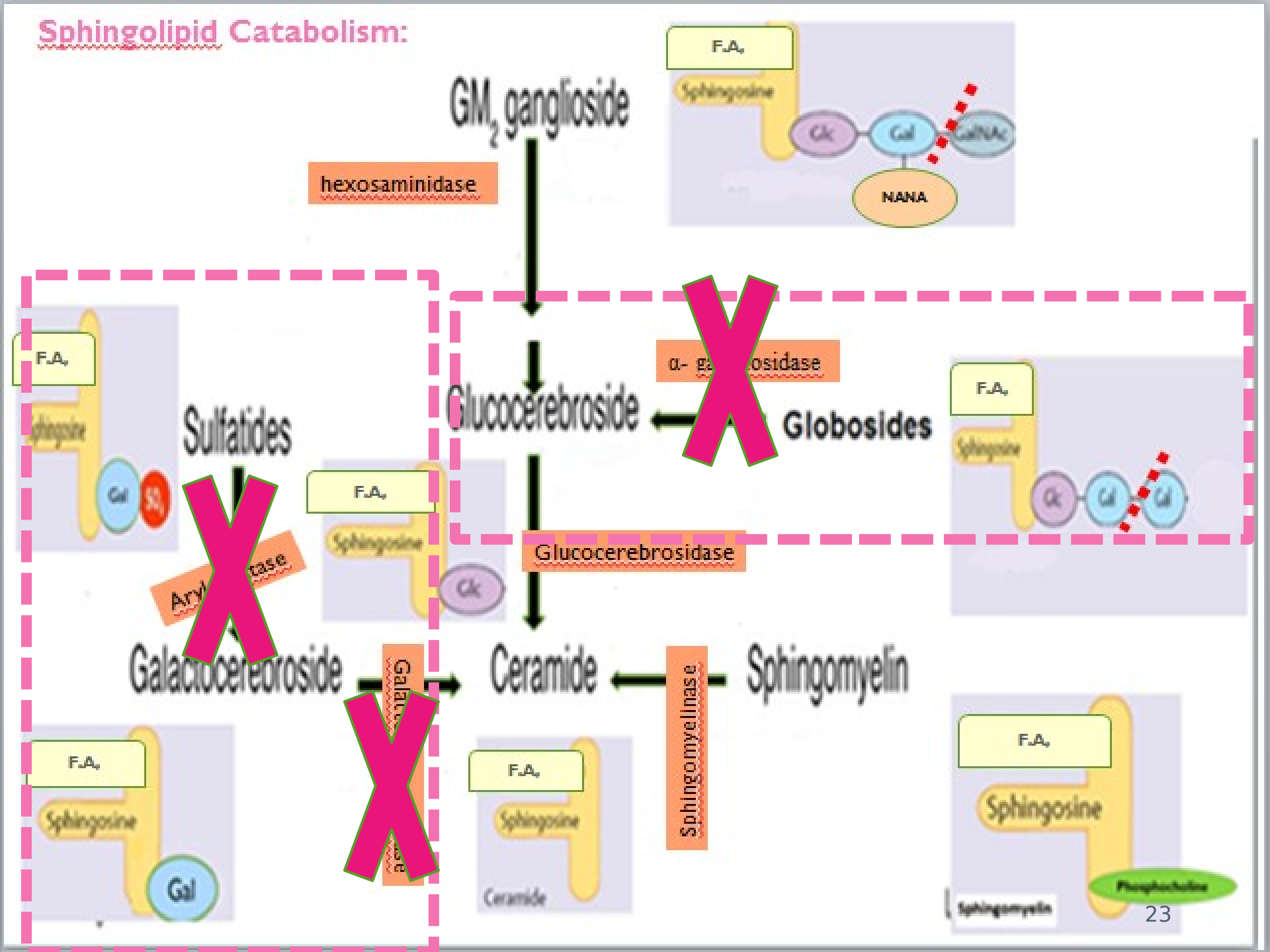
E. Synthesis of gangliosides

Disease	Deficient Enzyme	Accumulated Substrate	Manifestations
Tay- Sachs disease	Hexosaminidase A	Ganglioside GM2	Rapidly progressing Mental retardation & Blindness Cherry-red macula Muscular weakness & Seizures Early mortality
Gaucher's disease	β – Glucocerebrosidase	Glucocerebrosid	Hepatosplenomegaly Pancytopenia or Thrombocytopenia Long bone degeneration mental retardation in infantile form only
Niemann-Pick disease	Sphingomyelinase	Sphingomyelin	Mental retardation Hepatosplenomegaly Early death (A- type)

Other Lipid Storage Diseases:

FABRY DISEASE	METACHROMATIC LEUKODYSTROPHY	KRABBE DISEASE
https://www.aocd.org/page/FabryDisease	 https://scopeheal.com/metachromatic-leukodystrophy/	https://www.huntershope.org/family-care/leukodystrophies/krabbe-disease/

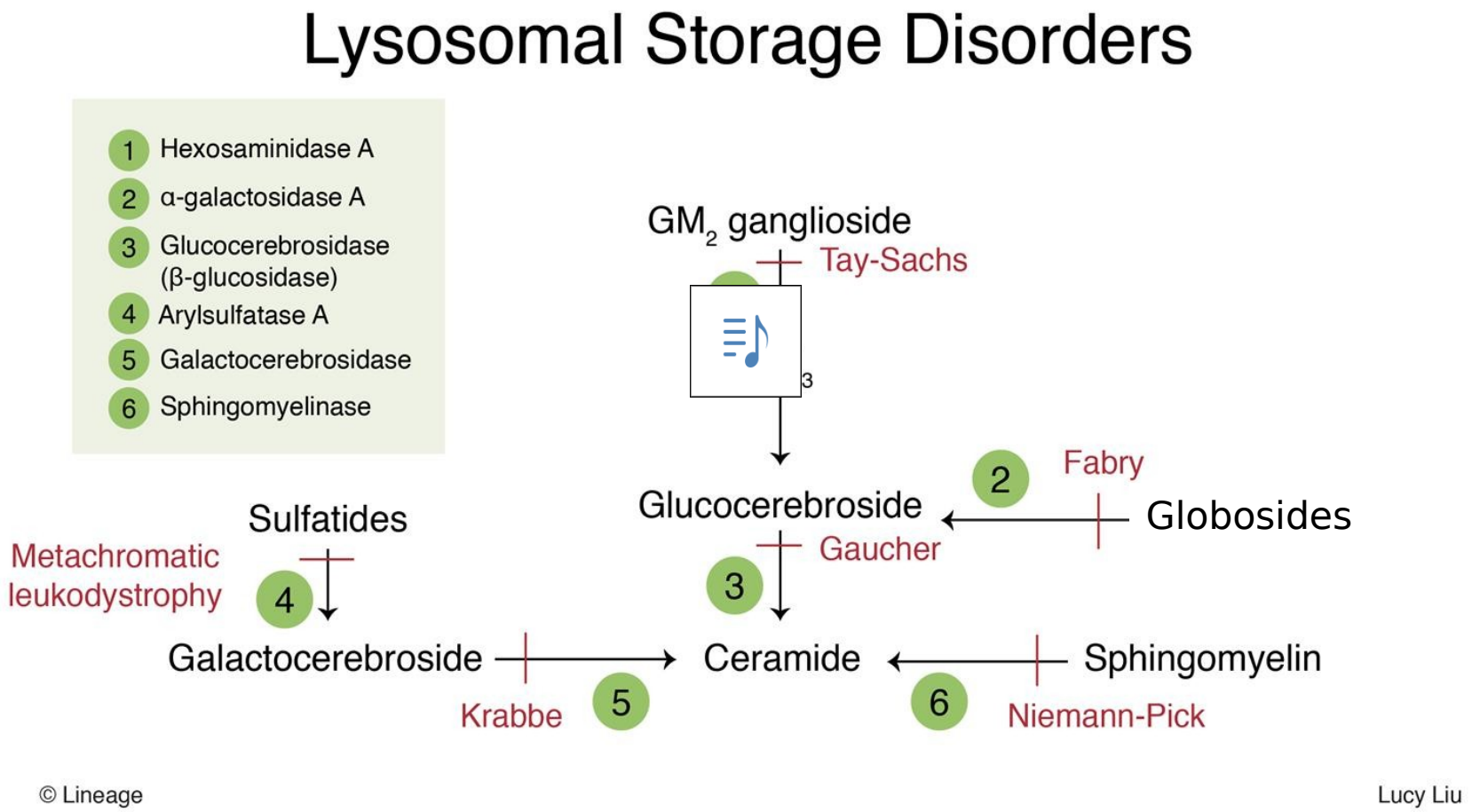
Sphingolipid Catabolism:



Other Lipid Storage Diseases:

Disease	Deficient Enzyme	Accumulated Substrate	Manifestations
FABRY DISEASE	α-galactosidase A	Globosides	• X linked • skin rash • Kidney and heart failure • ERT
METACHROMATIC LEUKODYSTROPHY	Arylsulfatase A	S des	• Cognitive deterioration • Progressive paralysis and dementia in infantile form.
KRABBE DISEASE	Galactocereb-rosidase	Galactocereb-osides	• Mental and motor deterioration • Blindness and deafness.

Other Lipid Storage Diseases:



Diagnosis of Sphingolipidos

- A specific sphingolipidosis can be diagnosed by one or more of the following:

1. Measuring **enzyme activity** in cultured fibroblasts or peripheral le cytes
2. **Analysis of DNA.**
3. **Histologic examination** of the affected tissue (shell-like inclusion bodies are seen in Tay-Sachs, and a wrinkled tissue paper appearance of the cytosol is seen in Gaucher disease)
4. **Prenatal diagnosis** , using cultured amniocytes or chorionic villi

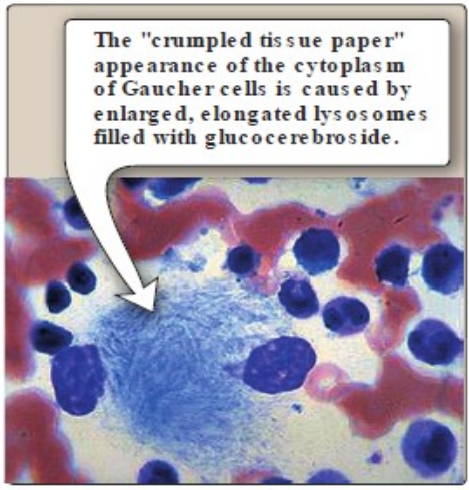
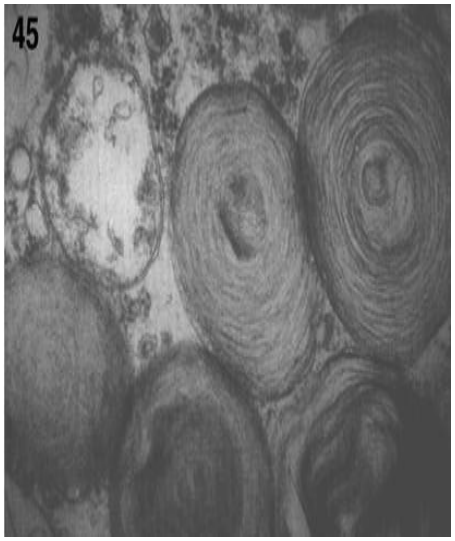

The "crumpled tissue paper" appearance of the cytoplasm of Gaucher cells is caused by enlarged, elongated lysosomes filled with glucocerebroside.

Figure 17.19
Aspirated bone marrow cells from a patient with Gaucher disease.



Electron micrograph in conjunctival biopsy showing typical membranous concentric bodies in Tay-Sachs disease

Lippincott's Illustrated Reviews: Biochemistry, Sixth Edition (2014)
.https://pdfs.semanticscholar.org/5935/020ad8e4a8a00f787c6579900035a15b3690.pdf

Treatment of Sphingolipidoses:

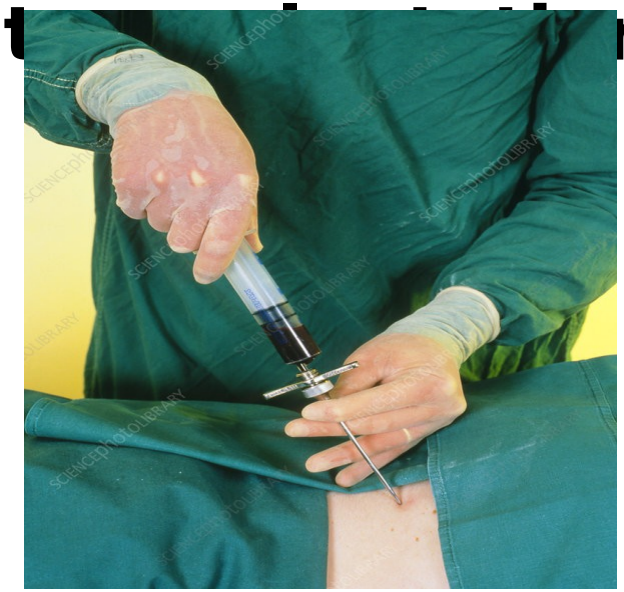
- There is no effective treatment for many of the diseases,
- Some success has been achieved with **enzyme replacement therapy** and **bone marrow transplantation** in the treatment of Gaucher's disease.
- **Gene therapy** for lysosomal disorders is currently under investigation.
- **Substrate Reduction Therapy** through pharmacologic reduction of the accumulated substrate.

Quiz

- **A patient diagnosed as having Gaucher's disease. What are the main two lines of TTT?**

Enzyme replacement therapy (ERT) and **bone marrow t[illegible]n (BMT)**

https://www.pediatrichomeservice.com/blog/understanding-infusion-enzyme-replacement-therapy/

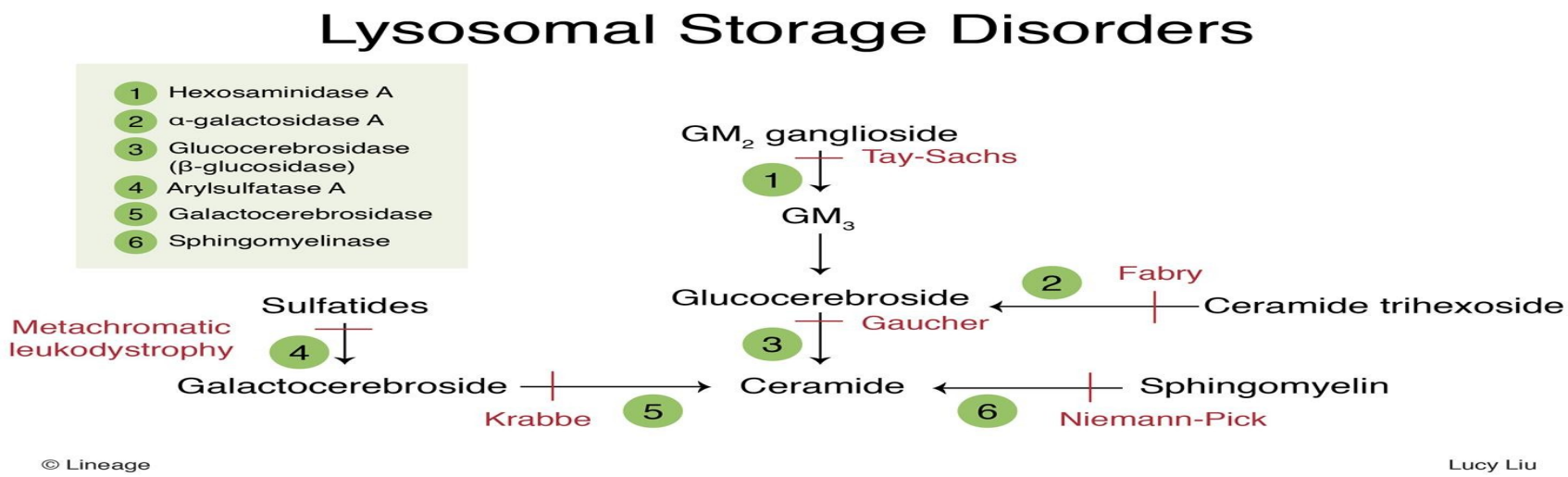


https://www.sciencephoto.com/media/278906/view/bone-marrow-transplant-harvesting-donor-marrow

Posterior superior iliac crest
The needle goes through the outer layer of the bone until it reaches the bone marrow space.
© AboutKidsHealth.ca

https://www.aboutkidshealth.ca/article?contentid=1530&language=english

Key Points



- Sphingolipidoses can be diagnosed by measuring enzyme activity or Analysis of DNA, Histologic examination of the affected tissue, or Prenatal diagnosis , using amniocentesis.
- There is no effective treatment for such diseases, However, enzyme replacement therapy and bone marrow transplantation showed some success. In addition to, Gene therapy and Substrate Reduction Therapy may be used

SUGGESTED TEXTBOOKS

- "Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R.Ferrier
- "Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W.Rodwell.
- Fundamentals of Clinical Chemistry (Tietz) Sixth
- "Textbook of Biochemistry with Clinical Correlations" by T.M.Devlin
- ***www.namrata.co- Biochemistry for medics***

many
Thanks!